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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,882	05/17/2006	Dominique Jean-Pierre Mabire	PRD-2124USPCT	8486

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EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	PAPER NUMBER
1614	
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11/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,882	MABIRE ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 6, 8, 10-30* is/are pending in the application.

4a) Of the above claim(s) *8,10-13 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,14-16,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/2/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of claim

Claims 5, 7, and 9 have been canceled and claims 1-4, 6, 8, 10-30 are currently pending.

Election/Restrictions

Applicants' election of group I including claims 1-4, 6, 14-16, and 29-30 and election of compound 2 as a single disclosed species of compounds defined by formula (I) , in the reply filed on 10/17/2008 are acknowledged.

Applicants argue that the process for making the compounds, Group VI can be examined together with the compound without requiring an additional search burden from the Examiner. This is not found to be persuasive since search burden being undue is a moot argument for lack of unity issue. Undue search burden is not an issue in a lack of unity. The requirement is still deemed proper and is therefore made final.

Claims 8, 10-13, and 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group. The elected species is free of prior art, thus examination is further extended the next species wherein X is N; n is 0, 1, or 2; R^1 is C_{1-6} alkyl; and R^2 taken together with R^3 forms =O, or when R^2 is hydrogen, R^3 is a group of formula (b-1) wherein t is 0 and Z is formula (c-2); and R^4, R^5 and R^6 are each independently hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy. Claims 1-4, 6, 14-16, and 29-30 are under examination in the instant office action.

Priority

The instant application is a 371 of PCT/EP04/013162 filed on 11/18/2004 and acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). A certified copy of foreign application filed on 11/20/2004 has been submitted on 5/17/2006.

The earliest effective U.S. filing date of the instant invention has been determined to be 11/18/2004.

Claim Objection

Claims 29-30 are objected as being dependent from the non-elected group.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 14-15, and 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R^1 as C_{1-6} alkyl and R^3 as formula (a-1), (a-2), (a-3), or -$(CH_2)_t$-Z-, wherein Z is formula (c-1), (c-2), (c-3), or (c-4), does not reasonably provide enablement for remaining scope wherein R^1 as thienyl and R^3 is –S-R^{11}, -CN, or heterocyclic ring systems other than formulae (c-1), (c-2), (c-3), and (c-4), which have additional substitutions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There is no reasonable basis for assuming that the myriad of compounds embraced by all

the generic claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- The claim is drawn to compounds defined by formula I, which are allegedly effective for inhibiting nuclear enzyme poly(ADP-ribose) polymerase (PARP). The formula I is drawn to substituents layered on top of substituents that vary independently and lead to compounds of a wide variety of structures. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, acidity, basicity, and properties that are known in the art to greatly influence pharmacokinetic and pharmacodynamic parameters, not to mention the ability to productively bind to claimed biological target molecules. The claims cover compounds easily in the millions given the number of possible rings, ring systems covered by the claims' scope along with varying choices for remaining variables;

2) Level of unpredictability in the art- The invention is pharmaceutical in nature as it involves interaction with to a particular type of poly(ADP-ribose) polymerase enzyme. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See *In re Fisher* 166 USPQ 18;

3) Direction or guidance- As stated above, the compounds made are not representative of the instant scope but are closer to each other than to remaining scope. In particular, R^3 can be a eterocyclic ring which have various structures with different numbers of heteroatom in various sizes. The presence of these various bulky heterocylic rings attached to quinolinone or quinoxalinone ring may be chemically incompatible with the method of use embraced in the instant claims. Specification offers no teachings or suggestion as to how to make and use these compounds. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.";

4) State of the prior art- The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. The compounds are substituted quinolinone or quinoxalinone derivatives with a heterocyclic ring bearing additional ring substitutions. No such compounds are known from a search in the prior art for even one use much less for activity relied on herein;

5) Working examples- The specification gives some *in vitro* test results on PARP inhibitory effects of limited number of preferable compounds, however it is too homogeneous to provide a clear evaluation of which rings attached to quinolinone or quinoxalinone with various substitutions out of the many claimed might affect potency to a large or small degree. The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. Extremely broad generalizations as found in the instant claims are in contradiction with the basis of quantitative structure-activity-relationship (QSAR).

6) The quantity of experimentation needed: In view of the above considerations, one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a compound out of the plethora of possibilities encompassed by the formula I that would have useful biological properties.

Genentech Inc. v. Novo Nordisk A/S (CA FC)42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

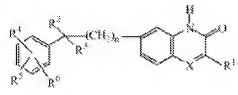
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

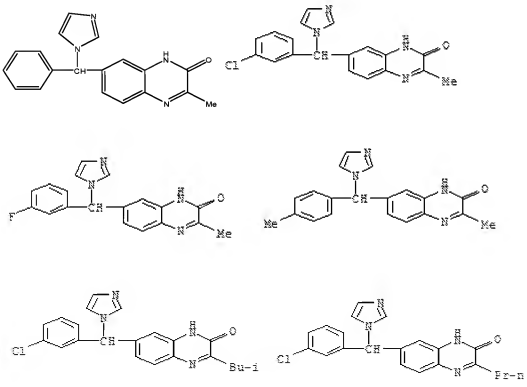
Claims 1-3, 6, 14-15, and 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US patent 5,028,606 (issue date: 7/2/1991).

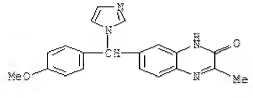
The instant invention is drawn to a compound of the following formula (I) and a pharmaceutical composition comprising the compound of formula (I) and a pharmaceutically acceptable carrier.

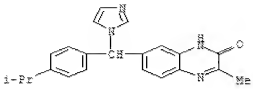


(I)

US 5,028,606 teaches substituted quinoxalinone derivatives (abstract and Table 9), encompassing the species of the instant compounds defined by formula (I), wherein X is N, n is 0, 1, or 2, R^1 is C_{1-6} alkyl; R^2 is hydrogen, R^3 is a group of formula (b-1) wherein t is 0 and Z is formula (c-2), and R^4, R^5 and R^6 are each independently hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy. The following compounds are some examples of substituted quinoxalinone derivatives disclosed in US 5,028,606, which are the species of the instant invention (Table 9, compounds 60, 81, 83, 84, 119, 179, 177, 124, and 174):







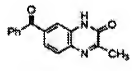
The reference also teaches a pharmaceutical composition of substituted quinoxalinone derivatives with a pharmaceutically acceptable carrier (column 20, lines 47-58).

Instant claims 29-30 are directed to a product made by the process of the instant claim 13. However, the product is the same compound of the prior art regardless of process of making, thus differences in the process of making the same compound do not have any patentable weight. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Thus, Claims 1-3, 6, 14-15, and 29-30 are anticipated by US 5,028,606.

2) Claims 1 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Ali *et al.* (Molecules 5:864-873, 2000). Ali *et al.* was supplied by Applicants in the IDS filed on 11/02/2006.

Ali *et al.* teach the following compound (p865, scheme I), encompassing the species of the instant compounds defined by formula (I), wherein X is N; n is 0, 1, or 2; R^1 is C_{1-6} alkyl; and R^2 taken together with R^3 forms =O, R^4, R^5 and R^6 are each independently hydrogen.



As stated above in the first 102 rejection, since the prior art teaches the same compound as the instant invention, the instant claim 29 is also anticipated by Ali *et al.* regardless of process of making.

As such, the instant claims 1 and 29 are anticipated by Cushman *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

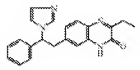
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

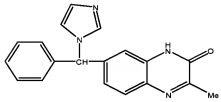
Claims 4 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,028,606 in view of Wolff (Burger's Medicinal Chemistry, 4th ed., p336-337, 1980)

The following compound is recited in the instant claim 4.



compound 1

US 5,028,606 teach the following compound as stated above in the first 102 rejection.



The difference between the instant compound and that of the prior art is that the instant compound has ethyl groups instead of methyl groups in the positions 7 and 3 of quinoxalinone ring.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute methyl group with ethyl group since it is routine experimentation to substitute one C_{1-5} alkyl group with another C_{1-5} alkyl group in the field of medicinal chemistry. To those skilled in the art of medicinal chemistry, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. *In re Henze*, 85 USPQ 261 (1950). Thus, one of ordinary skill in the art would have been

motivated to prepare homologues of the compounds taught in the reference with the expectation of obtaining compounds which could be used in pharmaceutical compositions. However, the examiner provides Wolff's reference. Wolff teaches that the addition of alkyl groups to active pharmacological agents often improves activity and bioavailability by increasing lipophilicity (see the examples in Table 8.2, p. 337 of a local anesthetic SAR). As such, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare homologues of compounds taught by US 5,028,606, with longer alkyl chains, as suggested by Wolff, to achieve better bioavailability or to improve activity.

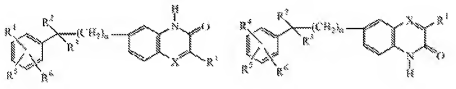
Provisional Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

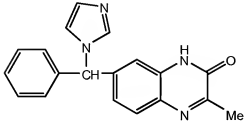
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

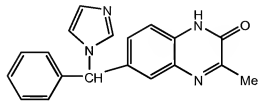
Claims 1-4, 6, 14-16, and 29-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 7 of copending Application No. 10/595891 in view of US 5,028,606. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to substituted quinolinone and quinoxaline compounds of the almost identical structure and the same substitutions. The difference between the instant compounds and the compounds of the '891 application is the position of the substitution (position 7 for the instant application and position 6 for the '891 application) as shown below:



As stated in the first 102 rejection above, US 5,028,606 teaches the same compounds as the instant invention. It further shows that position isomers, which have a substitution in the

either position 6 or position 7 of quinoxaline ring, are possible while retaining the same biological activity. The following is an example of positional isomers shown in US 5,028,606.





It would have been obvious to a person of ordinary skill in the art at the time the invention was made to change substitution position to get another positional isomer with a reasonable expectation of success since US 5,028,606 already suggests making positional isomers of the same core structure as the instant invention in the same positions while retaining the same biological activity. One skilled in the art would have been motivated to prepare positional isomers as taught by the prior art with the expectation of obtaining another homologous compound which will retain the same activity.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 8:00-5:00 Monday-Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BONG-SOOK BAEK
Examiner, Art Unit 1614

Bbs

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614